CHAPTER

EPIDEMIOLOGY OF OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCERS

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MAJOR CONTROVERSIES

- **What are the epidemiologic characteristics of ovarian cancer?**
- **What are the possible mechanisms of ovarian carcinogenesis?**
- **What factors are known to modify the risk of ovarian cancer in humans?**
- **How does parity affect the risk of ovarian cancer?**
- **What is the effect of oral contraceptives on ovarian cancer risk?**
- **Does age at menarche influence the risk of ovarian cancer?**
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Few aspects of gynecologic cancer are as fraught with controversy as are the issues related to the etiology of ovarian cancer. The past decade has seen a series of major advances in understanding the pathobiology of this clinically challenging malignancy, but much remains uncertain. This chapter reviews the highlights of ovarian cancer epidemiology and etiology, focusing on issues that are likely to be of interest to the practicing gynecology clinician.

What are the epidemiologic characteristics of ovarian cancer?

Although the vast majority of malignant ovarian tumors are epithelial in origin, cancers also can derive from the other cell types that are present in the ovary: tumors that develop from ovarian germ cells are classified as dysgerminomas and teratomas; tumors derived from follicular cells are designated sex cord–stromal

Table 24–1. Cumulative Probability (%) of Developing or Dying of Invasive Ovarian Cancer from Birth to the End of the Age Interval Specified

	All Women		White Women		Black Women	
Age (yr)	*Developing*	*Dying*	*Developing*	*Dying*	*Developing*	*Dying*
0-9	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
10-19	0.01	<0.01	0.01	<0.01	<0.01	<0.01
20-29	0.05	<0.01	0.05	<0.01	0.04	<0.01
30-39	0.12	0.01	0.13	0.01	0.08	0.01
40-49	0.29	0.06	0.30	0.06	0.19	0.05
50-59	0.60	0.19	0.63	0.20	0.36	0.14
60-69	1.00	0.42	1.06	0.45	0.63	0.31
70-79	1.41	0.73	1.51	0.79	0.91	0.53
80-89	1.67	0.98	1.77	1.06	1.06	0.65
90+	1.72	1.04	1.83	1.13	1.10	0.69

From Feuer EJ, Wun LM: DEVCAN: Probability of Developing or Dying of Cancer Software, Version 4.2. Bethesda, MD: National Cancer Institute, 2002.

tumors, most often granulosa cell tumors; and stromal elements of the ovary may give rise to sarcomas (e.g., fibrosarcoma). However, these malignancies are quite rare and, consequently, the incidence of epithelial ovarian cancer is generally approximated by the incidence of ovarian cancer as a whole.

In the United States, ovarian cancer accounts for 4% of newly diagnosed cancers in women, with 25,400 new cases expected during 2003; 14,300 deaths are expected to result from ovarian cancer in 2003, representing 5% of all female cancer deaths. The cumulative probabilities of developing, or dying from, ovarian cancer among U.S. women are 1.4% and 0.7%, repectively, by age 80 (Table 24-1). Although ovarian cancer is rare in women younger than 40 years of age, the incidence rises with increasing age and peaks in the fifth decade, after which the rate plateaus.[1] Because the majority of women who develop ovarian cancer eventually die of the disease, mortality rates vary with incidence rates (Table 24-2). Ovarian cancer incidence rates vary among different populations. Rates are highest among Caucasian women in Europe and the United States, with lower rates in women from Central and South America.[2] Latina women living in the United States have rates approaching those of white women from other ethnic groups. Asian women generally have lower rates, although these rates increase among individuals of Japanese or Chinese descent living in the United States.[3] The incidence of ovarian cancer is generally lower among black women in the United States than among white women (Tables 24-2 and 24-3).[4]

Epithelial ovarian neoplasms are commonly separated into "invasive" and "borderline" categories. The borderline tumors are also referred to as tumors of "low malignant potential," because of their lower histologic grade and more favorable disease prognostic characteristics. Approximately 20% of all ovarian neoplasms are borderline tumors.[5-7] Invasive ovarian cancers are further subclassified by histologic subtype. Serous histology is most frequently seen, accounting for 56% of ovarian cancers in a contemporary Canadian series.[8] Mucinous tumors are the second most frequent, at 18%, followed by endometrioid cancers (16%) and clear cell tumors (6%). Some consider the clear cell and endometrioid subtypes to have similar histogenetic origins, and at times these are grouped together. "Other, unclassified" and mixed epithelial tumors accounted for 3% of the total in the Canadian series. Incidence rates for the serous and endometrial subtypes

Table 24–2. Surveillance, Epidemiology, and End Results (SEER) Race-Specific, Age-Adjusted Incidence Rates for Invasive Ovarian Cancer (11 Registries, 1992–1999)*

Age (yr)	All Races	White	Black	American Indian/Alaska Native	Asian or Pacific Islander	Hispanic
All	17.1	18.1	12.2	8.7	12.6	13.2
0-19	0.8	0.8	0.6	0.7	1.1	0.9
20-29	4.0	4.1	3.2	1.1	4.2	4.4
30-39	7.8	8.2	4.4	3.7	8.0	5.8
40-49	17.6	18.6	11.8	9.9	15.6	13.7
50-59	32.6	34.7	20.8	16.8	27.7	24.6
60-69	46.7	50.3	33.7	16.5	30.0	37.4
70-79	58.6	62.2	48.9	30.2	31.1	42.7
80+	57.7	60.2	45.7	42.4	30.7	42.7

*Rates are expressed as cases per 100,000 women per year, age-adjusted to the U.S. population from the 2000 census.
From Ries L, Eisner M, Kosary C, et al: SEER Registries: SEER Cancer Statistics Review, 1973-1999. Bethesda, MD: National Cancer Institute, 2002.

Table 24–3. Surveillance, Epidemiology, and End Results (SEER) Race-Specific, Age-Adjusted Mortality Rates for Invasive Ovarian Cancer (Total United States, 1990–1999)*

Age (yr)	All Races	White	Black	American Indian/Alaska Native	Asian or Pacific Islander	Hispanic
All ages	9.2	9.5	7.8	4.9	4.7	5.7
0-19	0.0	0.0	0.0	0.0	0.0	0.0
20-29	0.2	0.2	0.3	0.4	0.2	0.3
30-39	1.1	1.1	1.1	0.9	0.9	0.9
40-49	4.8	5.0	3.7	3.3	3.9	3.2
50-59	14.3	14.9	10.8	7.3	9.6	9.2
60-69	28.9	29.9	24.5	15.9	14.3	17.2
70-79	45.8	47.0	40.5	21.9	18.1	26.8
80+	55.1	56.1	48.3	29.4	23.5	34.9

*Rates are expressed as cases per 100,000 women per year, age-adjusted to the U. S. population from the 2000 census.
From Ries L, Eisner M, Kosary C, et al: SEER Registries: SEER Cancer Statistics Review, 1973-1999. Bethesda, MD: National Cancer Institute, 2002.

peaks between the ages of 70 and 74 years; there is a slightly later peak for mucinous tumors, and a *much* earlier peak (ages 55 to 59 years) for clear cell tumors[9] (Table 24-4).

What are the possible mechanisms of ovarian carcinogenesis?

Incessant ovulation hypothesis. The "incessant ovulation" hypothesis of ovarian carcinogenesis, originally put forth in 1972 by Fathalla, postulated that the disruption and cellular injury in the ovarian epithelium that occurs with each ovulation requires time to heal appropriately and that, without an adequate rest period, the repair can become disordered, leading to neoplastic transformation.[10] Furthermore, each injury and repair cycle is thought to stochastically increase the opportunity for erroneous DNA repair. It has been postulated that some ovarian cancer risk modifiers, such as pregnancy and oral contraceptive (OC) use, reduce the "ovulation age" by providing a respite from ovulation, diminishing the need for repair to the ovarian surface epithelium, and thereby reducing the risk of ovarian cancer.[11,12]

Table 24–4. Histology-Specific, Age-Standardized Incidence Rates for Invasive Ovarian Cancer (Canadian Cancer Registry, 1991–1993)

Histologic Subtype	Rate*
All types, combined	13.71
Serous	4.61
Mucinous	1.72
Endometrioid	1.28
Clear cell	0.60
Other epithelial	3.57
Carcinoma not otherwise specified	1.29

*Age-standardized incidence rate per 100,000 women per year.
From Zhang J, Ugnat AM, Clarke K, Mao Y: Ovarian cancer histology-specific incidence trends in Canada 1969-1993: Age-period-cohort analyses. Br J Cancer 1999;81:152-158.

Ovulation is also linked to the formation of clefts and inclusion cysts, which are lined with ovarian epithelium and are found within the ovarian stroma. Ovarian cancer appears to arise from surface epithelium that is trapped within the ovarian stroma, rather than from the ovarian surface itself. Some authors propose that these inclusion cysts represent preneoplastic lesions, and that it is the proliferation and subsequent transformation of the ovarian epithelium lining these cysts that leads to cancer.[13] This theory is based on observations that the ovarian surface epithelium lining the clefts and inclusion cysts develops metaplastic changes with time. Rather than the normal squamous or cuboidal morphology, these cells take on a more columnar shape. They then become positive for markers found in ovarian neoplasia, such as CA 125 and E-cadherin. The cells lining these cysts have also been noted to develop histologic dysplasia and other morphologic signs of neoplastic progression.[14,15]

Gonadotropin hypothesis. The "gonadotropin hypothesis" derives support from both animal models and epidemiologic data. Pituitary hormones are required for ovarian tumor development in various rodent models. In these models, conditions that are characterized by a decrease in peripheral circulating estrogens, and a consequent increase in pituitary gonadotropin secretion, are associated with an increase in ovarian tumor development. Ovaries exposed to the chemical carcinogen dimethylbenzanthrene (DMBA) will develop tumors after they are transplanted into oophorectomized mice, but not if those mice have had their pituitaries removed.[16] Irradiated (hormonally inactivated) ovaries transplanted into rodent hosts with intact ovaries remain tumor free, but they often develop tumors if transplanted into oophorectomized hosts.[17]

Even in the absence of an external carcinogen, the incidence of ovarian cancer in rodents is markedly increased if both ovaries are implanted into the spleen.[18] The ovarian hormone secretions from intrasplenic ovaries enter the portal circulation and are then metabolized by the liver before entering the systemic circulation. The resulting decrease in peripheral

circulating estrogens triggers an increase in pituitary gonadotropin secretion. Under these conditions, the risk of malignant transformation within the intrasplenic ovaries is increased.[18] If circulating estrogen levels are maintained (through administration of supplemental estrogen or the retention of an ovary in its original, native position), these tumors do not develop, presumably because the estrogen suppresses gonadotropin secretion. Additional support for the gonadotropin hypothesis is found in the observation that exogenous gonadotropins speed the development of tumors in intrasplenic ovaries.[18]

Cramer and Welch[19] theorized that increased levels of gonadotropins are not directly mutagenic to the ovarian epithelium; rather, the elevated levels of gonadotropins induce ovarian secretion of estrogen, which then acts locally (in a paracrine manner) to induce proliferation and subsequent transformation of ovarian epithelium. The circulating hormones alter gonadotropin secretion, which in turn influences ovarian hormone secretion. Therefore, the reduction in ovarian cancer risk seen in parous women and subsequent to the use of OCs could be explained by the decreases in gonadotropin secretion that characterize these two states.

Androgen hypothesis. In 1998, Risch[20] put forth the hypothesis that androgens have an important role in the pathogenesis of ovarian cancer. This theory is based on evidence that ovarian epithelial cells contain androgen receptors and therefore should be capable of responding to androgenic signals.[21,22] The ovarian epithelium is exposed to androgenic steroids from both ovarian and adrenal sources, including androstenedione, dehydroepiandrosterone, and testosterone.[23] In vitro studies indicate that androgens can stimulate growth of normal ovarian epithelial cells in tissue culture,[24] as well as the growth of ovarian cancer cell lines.[25] Androgens have also been found to stimulate proliferation of ovarian epithelium in guinea pigs, leading to the formation of cysts, papillomas, and adenomas.[26]

Some epidemiologic data also support this hypothesis. For example, a population-based case-control study found higher levels of androgens (androstenedione and dehydroepiandrosterone) in women who subsequently developed ovarian cancer than in matched controls.[27] Polycystic ovary syndrome, which is characterized in part by increased levels of androgens, was associated with an increased risk of ovarian cancer in a large cohort study,[28] although data from another study failed to find such an association.[29] According to this hypothesis, the reduction in ovarian cancer risk that is associated with the use of OCs would be expected based on suppression of androgen levels.[30]

Progesterone hypothesis. In contrast to the risk-enhancing effect of androgens, Risch[20] found evidence of a *protective* role for progesterone in relation to ovarian cancer risk. Beginning with the observation that normal ovarian epithelium contains progesterone receptors,[22] Risch found support for this hypothesis in both animal and epidemiologic studies. For example, the domestic laying hen (*Gallus domesticus*), which is known to spontaneously develop epithelial ovarian cancer, has proved to be a useful animal model.[31] One study found the 3-year incidence of ovarian cancer in hens older than 2 years of age to be 24%.[32] Because inhibition of ovulation by feed restriction decreases but does not eliminate ovarian cancer risk in this model, strategies to alter risk independent of their effects on ovulation can be studied. In the anovulatory bird, the risk of ovarian cancer decreases further with the administration of a combination OC preparation, and it decreases even further if the birds are given progestin alone.[33] These results imply that the estrogenic component of combination OCs may blunt the protective effect associated with progestin administration.

Molecular studies performed in macaque monkeys provide additional support for this hypothesis. In this animal model, progesterone induces, and estrogen inhibits, apoptosis of ovarian epithelial cells. If estrogen and a progestin are given together, the combination produces an intermediate result.[34]

These animal data are consistent with observations that suggest an increased risk of ovarian cancer among postmenopausal women taking estrogen alone, which is somewhat tempered by the coadministration of progesterone.[35] Other epidemiologic data support a protective role for progesterone. Pregnancy, which is accompanied by markedly increased levels of progesterone, is associated with a decrease in ovarian cancer risk. Combination OCs contain progestational agents, and their administration is also linked with decreased risk of ovarian cancer.[36] Progestin-only OCs, which only partially (or incompletely) suppress ovulation, are nonetheless associated with decreased risk of ovarian cancer.[37] However, the use of depot medroxyprogesterone acetate, a long-acting progestational contraceptive, had no demonstrated effect on the risk of ovarian cancer in the one study that examined this relationship.[38]

What factors are known to modify the risk of ovarian cancer in humans?

How does parity affect the risk of ovarian cancer?

The protective effect of parity on ovarian cancer risk is well documented, with supporting evidence seen in both case-control and prospective cohort studies. For example, a pooled analysis of three European hospital-based case/hospital-based control studies found that parous women were at reduced risk of ovarian cancer compared with nulliparous women, with a relative risk (RR) of 0.7 (95% confidence interval [CI], 0.6 to 0.8).[39] In this analysis, women reporting four or more term pregnancies had a 40% reduction in risk when compared with nulliparous women.

Subsequently, a collaborative analysis of multiple U.S. case-control studies was published.[40] The Collaborative Ovarian Cancer Group combined data at the individual subject level from 12 studies, which involved a total of 2197 ovarian cancer cases and 8893 controls. Six of the studies had hospital-based controls, and the remainder used various population-based methods for

ascertaining controls. For population studies, parous women had a marked decrease in the risk of ovarian cancer, with an odds ratio (OR) of 0.5 (95% CI, 0.4 to 0.6). Although data from the studies with hospital-based controls yielded evidence of a more modest protective effect, with a pooled OR of 0.8 (95% CI, 0.6 to 0.9), this discrepancy was largely accounted for by differences in parity between the study populations. The fitted OR per full-term pregnancy was similar across the different study populations, with an OR of 0.81 per pregnancy for population studies, compared with 0.87 for hospital studies. Therefore, each additional pregnancy reduced the risk of ovarian cancer by 13% to 19%. Risk also decreased with increasing parity in both study populations. Population-based data indicated that the greatest protection was associated with the first full-term pregnancy.

The association of parity with a decreased risk of ovarian cancer has also been confirmed in prospective cohort studies. Analysis of data from the Nurses' Health Study, for example, revealed that parous women overall had a 45% reduction in risk when compared with nulliparous women. In addition, the benefit seen increased with increasing parity, so that (in one model) each birth was associated, incrementally, with a 16% reduction in ovarian cancer risk.[41] It is unclear, at present, whether the effects of gravidity and parity are independent or are simply two different measures of the same basic association.

What is the effect of oral contraceptives on ovarian cancer risk? The effect of OCs on ovarian cancer risk has also been extensively evaluated in both case-control and cohort studies. Case-control studies have estimated risk reductions ranging from 30% to 60% for ever-users versus never-users.[40,42] A meta-analysis found that risk decreased with increasing duration of OC use. One year of OC administration was associated with an 11% reduction in risk, whereas 5 or more years' exposure decreased the risk by 50%,[43] an estimate that was confirmed in a subsequent study.[44]

Multiple cohort studies have also confirmed the ovarian cancer risk reduction associated with OC use.[35,45] In the Oxford Family Planning Association study, for example, the risk of ovarian cancer was decreased by 60% among those who had ever used OCs, with a significant trend for decreasing risk with increasing duration of use.[45]

Does age at menarche influence the risk of ovarian cancer? Although the previously cited pooled analysis of 12 U.S. case-control studies demonstrated a weak trend of decreasing ovarian cancer risk associated with increasing age at menarche, this finding was not confirmed in other case-control[42,46] or cohort studies.[41] Therefore, age at menarche cannot be considered an established risk factor for ovarian cancer, based on currently available data.

Is there a relationship between lactation and ovarian cancer risk? A modest protective effect for breast-feeding was demonstrated in population-based case-control studies. A 19% risk-reduction was seen among parous women who breast-fed, and the association persisted after adjustment for parity.[40] A larger protective effect of breast-feeding was seen in an Italian case-control study, with risk decreased by 50% among those who breast-fed for at least 12 months. This association persisted after adjustment for covariates (95% CI, 0.4 to 0.8).[42] Although a crude risk reduction of 29% with lactation was seen in an Australian case-control study, this effect failed to reach significance when adjusted for parity.[47] It is likely that breast-feeding is associated with, at best, a modest decrease in risk of ovarian cancer, although the data on this subject are sparse.

What are the effects of age at menopause and gynecologic surgery? Although a few European case-control studies found a modest increase in ovarian cancer risk with increasing age at "natural"(i.e., non-surgical) menopause,[46,48] other case-control studies found no evidence for such an effect.[40,42] Two large cohort studies[35,41] also found no relationship between age at menopause and risk of ovarian cancer. A meta-analysis combining data from six population-based case-control studies showed a weak association, which was not statistically significant (hazard ratio [HR], 1.1; 95% CI, 1.0 to 1.2).[49]

However, hysterectomy without complete oophorectomy has been associated with an estimated ovarian cancer risk reduction of 33% to 36% in various studies.[40,50,51] In addition, data from both cohort and case-control studies indicate a significant effect of tubal ligation (with retention of the ovaries) on ovarian cancer incidence and mortality. In the Nurses' Health Study, the incidence of ovarian cancer was found to decrease by 67% after tubal ligation.[51] Another study, using ovarian cancer *mortality* as the end point, found a significant protective effect after tubal ligation, with mortality decreasing by one third.[52]

Case-control studies estimate a more modest reduction in risk associated with tubal ligation. A cancer center–based case-control study showed a 48% risk reduction,[53] whereas a large Australian case-control study estimated the reduction in risk to be 39%.[50] A smaller World Health Organization study showed a 28% decreased risk, which failed to reach statistical significance.[54]

The mechanism for the decrease in risk associated with either of these gynecologic surgeries is not clear. Some have argued that the risk reduction seen is actually an artifact resulting from screening of the ovaries for cancer during these elective procedures. If this were true, however, one would expect diminishing benefit with increasing time since the surgery, and this is not seen. Others have asserted that both hysterectomy and tubal ligation decrease the access of talc (or other putative environmental carcinogens) to the ovary. The relative risk associated with perineal talc use has been estimated to be 1.3, with a minority of women reporting talc exposure. Therefore, the magnitude of the benefit that is seen with tubal ligation and hysterectomy is greater than what could be accounted for simply by removal of the putative talc-related risk alone.

Still others have postulated that these procedures may lead to a decrease in ovarian function and ovulation, perhaps through an alteration in ovarian circulation. Although the major blood supply to the ovaries is left intact as a result of these procedures, and there is no evidence that tubal ligation is associated with decreased levels of circulating ovarian hormones, there are no data on hormone levels in the microenvironment of the ovary after these surgeries. In addition, most studies of ovarian function after tubal ligation have limited follow-up to the first 12 months after the procedure, so little is known of long-term hormonal effects. In one report,[65] the decrease in breast cancer mortality associated with tubal sterilization argues for an alteration in ovarian steroidogenesis after the procedure; a second study failed to confirm this observation.[56]

Is there an association of menopausal hormone therapy with ovarian cancer? The effect of menopausal hormone therapy (MHT, also called estrogen replacement therapy or hormone replacement therapy) on ovarian cancer risk has been debated. Findings from various case-control studies have been contradictory, with some studies supporting an increased risk of ovarian cancer with MHT[39,48] and others finding no significant association.[40,57] An early meta-analysis suggested that the association between MHT and ovarian cancer was statistically significant,[58] but a later meta-analysis argued to the contrary.[59]

Prospective cohort studies have helped to clarify this situation. Analysis of a cohort of 211,581 women selected from the original cohort of the American Cancer Society Cancer Prevention Study II found that ever-users of MHT had an RR for ovarian cancer death of 1.2 (95% CI, 1.1 to 1.4), compared with never-users. Risk increased with increasing duration of estrogen use, such that those who used estrogen for greater than 10 years had 2.2 times the risk of death from ovarian cancer than those who never took MHT (95% CI, 1.5 to 3.2).[36]

In addition, data from the follow-up study of the participants in the Breast Cancer Detection Demonstration Project showed that in those who had ever taken MHT (in the form of estrogen given without a progestin) had an ovarian cancer RR of 1.6 (95% CI, 1.2 to 2.0). Risk also increased with increasing duration of use, such that those who took estrogen for 20 years or longer had a risk more than three times greater than that of never-users (RR, 3.2). The addition of progesterone to the hormone regimen appeared to modulate the risk downward. The group of women who had a progestin added after initial treatment with estrogen alone showed only a trend toward increased risk, with an RR of 1.5 (95% CI, 0.9 to 2.4). Among those women who took *only* the combination of estrogen and progestin, there were but 18 ovarian cancer deaths (in 42,400 person-years of follow-up), and no significant alteration of risk was demonstrated.[35]

Therefore, the weight of the more recent evidence, derived from the methodologically superior prospective cohort study design, suggests that MHT, particularly estrogen alone, is associated with a modest but significant increase in the risk of ovarian cancer. Although these data suggest that the combination of estrogen and progesterone may be safer than estrogen treatment alone in regard to ovarian cancer risk, long-term administration of this combination regimen is no longer considered appropriate in the routine health maintenance of postmenopausal women. A large randomized, controlled trial of a combination of oral estrogen with progesterone (versus placebo) was halted early because of an excess of adverse events (e.g., breast cancer, stroke, pulmonary embolus, coronary heart disease) in those taking the active drug.[60] For this reason, a new study of the effects of long-term combination MHT on ovarian cancer risk can no longer be contemplated, and all further data on this issue will have to come from follow-up of previously defined cohorts.

Is infertility a risk factor for ovarian cancer? There are conflicting reports regarding the effect of infertility on ovarian cancer risk. Women with fertility problems often differ from those without such problems in terms of other established ovarian cancer risk factors, such as parity or OC use. This issue is further complicated by the need to separate the biologic effects of infertility alone from the effects of the medications used to treat this condition. Initial case reports of ovarian cancer associated with ovulation induction prompted concern, because the medications used to stimulate ovulation act by increasing gonadotropin levels. Both the incessant ovulation hypothesis and the gonadotropin hypothesis predict that the use of these medications can lead to increased risk of ovarian cancer.

The oral agent clomiphene citrate, for example, produces an increase in pituitary gonadotropin secretion, which in turn stimulates ovulation.[61] Gonadotropin therapy, consisting of various formulations of follicle-stimulating hormone (FSH), or FSH and luteinizing hormone (LH), is given by injection to stimulate ovulation. If it is the trauma of ovulation alone that leads to an increased risk of ovarian cancer, one might expect an increased incidence of ovarian cancer among those women who responded to treatment with multiple ovulations, particularly those who used the medications for multiple cycles. If, instead, it is elevated levels of gonadotropins that increase then risk, then women who have been treated with any of these medications could be at increased risk.

The initial case reports were followed by the publication of case-control data indicating that infertile women who used fertility drugs had an elevated risk of ovarian cancer when compared with women without a diagnosis of infertility.[40] Women who had not used fertility medications showed no alteration in risk. In 1994, a study of a cohort of infertile women was published. Among the 3837 women studied, there were 11 cases of ovarian cancer, compared with the 4.4 cases that were expected. Of those 11 cases, 4 were invasive epithelial cancers, 5 were epithelial ovarian tumors of borderline malignancy, and the remaining 2 were granulosa cell tumors. More than half of the women in the cohort had been treated with clomiphene, but fewer

than 4% had received gonadotropin therapy. Although any use of ovulatory stimulants was associated with an increased risk of ovarian cancer, this increase was most dramatic among those women who had used clomiphene for more than 12 cycles, with an RR of 11 (95% CI, 1.5 to 81.3).[62]

Other studies attempted to clarify the effects of infertility medications on ovarian cancer risk by examining women who were referred for infertility treatment. An Australian study[63] of women who had been referred to a clinic specializing in in vitro fertilization found no evidence of an increased incidence of ovarian cancer in the entire cohort. Additionally, both those who had received fertility medication and those who had not had similar risks.

A meta-analysis[64] of eight case-control studies found that fertility drug use in *nulligravid women* was associated with an elevated risk of *borderline tumors*, but the risk of invasive ovarian cancer was not elevated. Nulligravid women who had attempted to become pregnant for more than 5 years had a 2.7-fold increased risk of ovarian cancer, compared with those who tried to conceive for less than 1 year. Among those who were nulliparous but who had been pregnant, fertility drug use was not associated with increased risk.

Effects of parity and other reproductive risk factors also make interpretation of the effect of infertility on the risk of ovarian cancer difficult to isolate. For example, in one case-control study, a higher proportion of cases than controls reported a history of infertility, giving a crude OR of 1.5, but cases were also more likely to be nulliparous and less likely to have taken OCs. In addition, only 43% of cases and 52% of controls knew their fertility status. After adjustment for these important covariates, the increased risk associated with long-term infertility was no longer significant. A subgroup analysis indicated that nulliparous women who reported infertility but had not been treated for it had a risk of ovarian cancer that was 2.5 times that of nulliparous women who did not report infertility.[65] In contrast, difficulty becoming pregnant was reported by 14% of women in one cohort study, with 17% of those nulligravid. The incidence of death from ovarian cancer was not increased in the infertile women.

An Israeli study[66] that was suggestive of an increased incidence of ovarian cancer in a cohort of infertile women observed only 12 cases among 2496 study subjects; the result was not statistically significant (standardized incidence ratio [SIR], 1.6; 95% CI, 0.8 to 2.9). The authors of the study noted that the observed difference in ovarian cancer incidence could be explained if half the cohort were nulliparous. In addition, there was no significant difference in incidence of ovarian cancer between those women who were treated with ovulatory stimulants and those who were not.

In summary, there is little convincing evidence that infertility itself increases the risk of ovarian cancer. Among women treated with ovulatory stimulants, there is evidence of an increased incidence of ovarian tumors of borderline malignancy, but thus far the evidence does not support an increased risk of invasive epithelial ovarian cancer.

Does exposure to psychotropic medications affect the risk of ovarian cancer? Psychotropic medications, such as amphetamines, sedatives, barbiturates, anticonvulsants, antidepressants, and antipsychotics, have been inconsistently associated with an increased risk of ovarian cancer. A case-control study from New England found that use of any of these medications for at least 6 months was associated with increased ovarian cancer risk, with an RR of 1.6 (95% CI, 1.1 to 2.3). This association was largely limited to medications that act through dopaminergic or GABAergic mechanisms, as opposed to serotoninergic medications.[67] However, another case-control study failed to corroborate this association.[68]

Data from a large cohort study did suggest a modest increase in the risk of ovarian cancer with the use of any psychotropic medication, as reported at the time of the baseline questionnaire (RR, 1.5). However, these results failed to reach statistical significance because of the small number of incident cases (47); the resulting 95% CIs were quite wide, 0.7 to 3.2.[69]

Do certain analgesic medications reduce the risk of ovarian cancer? The effect of analgesics such as acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAIDs) on ovarian cancer risk remains controversial. Case-control studies have provided conflicting evidence of a protective effect for acetaminophen. One study examined the relationship between continuous use of "analgesic medications" (defined as intake of aspirin, acetaminophen, or ibuprofen at least weekly, for 6 months or longer) and ovarian cancer risk. The analysis revealed no significant effect of either aspirin or ibuprofen consumption on ovarian cancer risk but did suggest a significant protective effect for the use of acetaminophen, with an adjusted OR of 0.5 (95% CI, 0.3 to 0.9).[70] Experimental studies in rodents demonstrating uterine and ovarian atrophy at high doses of acetaminophen, and decreased ovarian-cyst formation at lower doses, suggested a biologic basis for this observation.[71] Another case-control study found a similar risk reduction with acetaminophen use, with an OR of 0.6 (95% CI, 0.3 to 0.9).[72] However, two other case-control studies found little evidence of a relationship between acetaminophen intake and ovarian cancer risk.[73,74] The reason for these conflicting results is not clear.

Data from various cohort studies are also contradictory. One study suggested a 45% decrease in the risk of ovarian cancer death with daily acetaminophen use, but the finding failed to reach statistical significance.[75] Two other cohort studies found no evidence of a relationship between acetaminophen intake and ovarian cancer risk.[76,77]

Some of these same studies also analyzed the effect of aspirin use on risk and found no significant association.[70,72,73,76] A 40% to 50% risk reduction associated with intake of NSAIDs was seen in some studies,[73,76] but others found no such relationship.[70,74]

In summary, there are insufficient data in support of a protective effect of acetaminophen or NSAIDs to recommend the clinical use of these agents to reduce the risk of ovarian cancer. Further studies are needed to clarify this association, which, if real, would have significant clinical implications.

Is talc exposure an ovarian cancer risk factor? A number of case-control studies have found that application of talc to the perineum is associated with an increase in the risk of ovarian cancer. A meta-analysis of case-control studies found a modest increase in ovarian cancer incidence among women who reported exposure to talc (adjusted RR, 1.3; 95% CI, 1.1 to 1.5).[78] Similar increases in ovarian cancer risk, ranging from 1.3 to 1.5, were found in three additional case-control studies published after the meta-analysis.[47,79,80] Subsequently, Ness and colleagues[81] reported case-control data indicating an increased risk of ovarian cancer associated with conditions potentially related to ovarian inflammation, including talc use.

An association between the use of talc and an increased risk of ovarian cancer was not supported by analysis of the Nurses' Health Study, which collected prospective data from a cohort of more than 78,000 women. Although 40% of the cohort reported ever using talc, fewer than 15% reported ever using talc on a daily basis. Ever-use of perineal talc did not increase the risk of ovarian cancer (RR, 1.1; 95% CI, 0.9 to 1.4), and the risk was not increased with daily use. Theorizing that women who had undergone a tubal ligation or hysterectomy could be considered to be relatively protected from ovarian exposure to talc, the analysis was repeated excluding those women, but the association between talc exposure and ovarian cancer risk remained null (RR, 0.97; 95% CI, 0.7-1.3).[82]

Reports that the National Toxicology Program intended to review talc for possible listing in the 10th edition of the *Report on Carcinogens* triggered much debate. The International Agency for Research in Cancer (IARC) had previously designated talc containing asbestiform fibers as a human carcinogen but had indicated that the evidence regarding cosmetic (nonasbestiform) talc was insufficient.[83] The IARC also asserted that there was inadequate evidence for carcinogenicity to animals from any type of talc.[83] The National Toxicology Program indicated that studies published subsequent to the IARC review provided sufficient further evidence that talc is carcinogenic to humans to merit a listing in the 10th edition of the *Report on Carcinogens.* These studies suggested an association between exposure to talc in occupational settings and cancer risk in humans, as well as an association between use of talcum powder and cancer risk. However, at this time, the National Toxicology Program has deferred action on this listing and has indicated a need to establish a clear definition of the agent or agents in talc that are involved in human exposure.[84]

Overall, the aggregate data related to talc exposure are most reasonably interpreted as suggesting that the risk, if present, is small.

To what extent does family history contribute to the risk of ovarian cancer?

Family history of ovarian cancer. A family history of ovarian cancer has long been recognized as a risk factor for developing the disease, but estimates of the magnitude of this risk have varied. An Australian case-control study[47] demonstrated that ovarian cancer risk was significantly increased among women who had a first-degree relative with a history of ovarian cancer (RR, 3.9; 95% CI, 1.6 to 9.7); the RR increased to 4.8 when corrected for parity. In a pooled analysis of seven case-control studies, 4% of ovarian cancer patients had a history of ovarian cancer in first-degree relatives. This family history was associated with a substantial increase in ovarian cancer risk, compared with no such family history (RR, 5.4; 95% CI, 3.5 to 8.4).[44] A study of a cohort of first-degree relatives of ovarian cancer patients showed no increased risk of cancer, all sites combined, but did document an increased the incidence of ovarian cancer (SIR, 2.8; 95% CI, 1.8 to 4.2). The risk seemed higher if the affected relative was a sister (SIR, 3.7; 95% CI, 2.3 to 5.7) rather than a mother (SIR, 0.6; 95% CI, 0.0 to 3.1).[85]

Analyzing all previously published ovarian cancer case-control and cohort studies, a meta-analysis from 1998 found a pooled RR of 3.1 (95% CI, 2.6 to 3.7) for first-degree relatives of ovarian cancer cases. A gradient in risk was observed among specific classes of first-degree relatives: mothers of ovarian cancer patients were at least risk (RR, 1.1; 95% CI, 0.8 to 1.6), sisters were at higher risk (RR, 3.8; 95% CI, 2.9 to 5.1), and daughters appeared to have the highest risk (RR, 6.0; 95% CI, 3.0 to 11.9). In addition, risk increased with increasing number of affected family members. With one first-degree relative affected, the cumulative risk of developing ovarian cancer by 75 years of age was estimated to be 4.0%; with two affected relatives, the risk increased to 14%. For reference purposes, the analogous figure for women with no family history was less than 1%.[86]

Several attempts have been made to explore the question of whether the ovarian cancer risk factors identified from epidemiologic studies of unselected women with ovarian cancer behave in a similar fashion among ovarian cancer patients who have a positive family history of the disease. A cohort study examined the association of parity and ovarian cancer risk in individuals stratified by family history and found that nulliparous women with a family history were at higher risk of ovarian cancer than parous women with a family history of the disease, the same pattern previously observed in general population studies.[87] A population-based case-control study found that the risk of ovarian cancer was decreased by 50% in women with a family history of the disease who had used OCs for at least 4 years, again paralleling the general population data.[88] A large Italian case-control study suggested that women with both the standard risk factors and a family history were at greater risk than those with one, the other, or neither.[48] These analyses did not take into account the presence or absence of germline mutations in the ovarian cancer susceptibility genes.

Which genetic syndromes are associated with ovarian cancer?

BRCA1 and BRCA2. Between 5% and 10% of ovarian cancers are considered hereditary in origin, the result of germline mutations in cancer predisposition genes. Most of these cancers are part of the syndrome known as hereditary breast and ovarian cancer (HBOC) and can be attributed to germline mutations in the genes *BRCA1* or *BRCA2*. Both *BRCA* genes follow an autosomal dominant mode of inheritance and fit a tumor suppressor model of action. *BRCA1* is a large gene found on the long arm of chromosome 17.[89] The lifetime risk of ovarian cancer for women carrying a mutated form of *BRCA1* has been estimated at 40% to 60%,[90-92] with a lifetime risk of breast cancer approaching 90% in some families.[92,93] Female carriers of *BRCA1* mutations also have a risk of fallopian tube carcinoma estimated at 50 to 120 times that of the general population,[90,94] as well as a marked increase in the risk of primary peritoneal cancer (RR, 45).[90]

Study of HBOC kindreds with no evidence of linkage to the *BRCA1* gene led to the discovery of a second predisposition locus on chromosome 13, designated *BRCA2*.[95] Like *BRCA1*, *BRCA2* is a large gene with multiple documented disease-associated mutations scattered across its span. A region within exon 11 of *BRCA2* has been designated the "ovarian cancer cluster region," because mutations within this area are more likely to be statistically associated with ovarian cancer. The lifetime risk of ovarian cancer for female carriers of *BRCA2* mutations is lower than that reported for *BRCA1*, having been estimated at 16% to 27%.[92] Ovarian cancer in *BRCA2* mutation carriers tends to occur at a later age than in those with *BRCA1* mutations (57.5 versus 51.2 years).

Estimates of penetrance of the *BRCA* genes vary according to the population studied. Initial estimates were based on cancer incidence in the families used for linkage analysis and gene-finding, which were selected because of the occurrence of multiple cases of breast and ovarian cancer in multiple generations. In contrast, significantly lower penetrance estimates are found in studies that target populations that are more similar to the general population.

HNPCC. Ovarian cancer is also part of the spectrum of cancers seen in the hereditary nonpolyposis colorectal cancer syndrome (HNPCC). HNPCC is an autosomal dominant disorder that is associated with defects in the genes responsible for DNA mismatch repair. Although HNPCC is most characteristically associated with early-onset colon cancers, it is also characterized by increased risks of a number of extracolonic malignancies, including cancers of the endometrium and ovary, as well as cancers of the stomach, small bowel, and upper urinary tract. The cumulative risk of ovarian cancer by age 70 years among persons with mutations in one of the mismatch repair genes is approximately 12%,[96] compared with the general population risk of 1.4%. Although these risks are not as dramatically elevated as those associated with *BRCA1/2*, they are still 8 to 9 times higher than the expected risks among women in the general population.

Other familial cancer syndromes. The *Carney complex*, a syndrome clinically manifested by primary pigmented nodular adrenal disease, cardiac and skin myxomas, blue nevi, and endocrine disorders, has been associated with ovarian tumors, including both adenomas and adenocarcinomas.[97] *Peutz-Jeghers syndrome*, characterized by pigmented lesions on the lips, gastrointestinal hamartomatous polyps, and mutations in the *STK11* gene, is associated with an incidence of carcinoma estimated at 20% to 50%. Although gastrointestinal cancers are the most common malignancy associated with this syndrome, affected females may develop ovarian neoplasms. Tumors arise from the ovarian surface epithelium or from ovarian stromal cells, and they include the sex cord tumor with annular tubules, Sertoli cell tumors of the ovary, and mucinous epithelial ovarian cancers.[97] Ovarian carcinoids have been reported in association with the *multiple endocrine neoplasia type 1* syndrome. This syndrome is more characteristically associated with parathyroid adenomas and secretory tumors of the pancreas or gastrointestinal tract.[97] Juvenile granulosa cell tumors of the ovary have been associated with *Ollier's disease* enchondromatosis) in several case reports.[98] The *nevoid basal cell carcinoma syndrome*, which has been linked to the gene *PTCH*, is associated with an increased incidence of ovarian fibromas.[99] Further details regarding the hereditary ovarian cancer syndromes are presented in Chapter 62.

What are the epidemiologic characteristics of primary carcinoma of the fallopian tube?

Primary carcinoma of the fallopian tube is extremely rare, with an annual incidence estimated at 3.6 per 1,000,000 women per year in the United States.[100] The incidence of fallopian tube cancer increases with advancing age, with little risk before age 25 years; the incidence peaks between 60 and 64 years of age. In 20% of cases, cancer of the fallopian tube is diagnosed simultaneously with a cancer of another site.[100] Because the diagnosis of primary carcinoma of the fallopian tube is made so infrequently, it is often grouped together with ovarian neoplasms in statistical databases. In a population-based dataset, women with fallopian tube carcinoma had better survival, stage for stage, than did women with epithelial ovarian cancer.[101] Although a number of investigators have published case series of patients with fallopian tube carcinoma in which the clinicopathologic characteristics of this cancer are summarized,[102-104] to date no systematic studies designed to assess risk factors have been published.

There has been a resurgence of interest in this rare cancer with the realization that carriers of mutations in the *BRCA* genes are at increased risk of primary carcinoma of the fallopian tube. Case reports have linked fallopian tube carcinoma with germline mutations in both *BRCA1*[105,106] and *BRCA2*.[107] A Canadian study[108]

found that 7 women from a population-based series of 45 cases of fallopian tube cancer were carriers of *BRCA* mutations. In some cases, investigators have demonstrated loss of heterozygosity at the wild-type *BRCA1* allele in these tumors, evidence supporting an etiologic link between the *BRCA* mutation and the development of the fallopian tube malignancy.[106] In addition, two studies have demonstrated a dramatically increased risk for this disease among *BRCA1* carriers, with estimated RRs between 48 and 120.[90,94]

The most pragmatic consequence of recognizing that the fallopian tube is one of the organs at risk for malignant transformation in women with germline mutations in *BRCA1* or *BRCA2* is the need to consciously include the fallopian tube when performing risk-reducing bilateral oophorectomy. It would be imprudent at best to leave some or all of the fallopian tube behind when attempting a surgical procedure that has cancer risk reduction as its primary goal. Optimal surgical technique assumes even greater importance now that most of these procedures are done laparoscopically. Special attention must be paid to avoid leaving a remnant of ovarian tissue at the distal end of the utero-ovarian ligament, and the proximal end of the fallopian tube should be transected as close to the uterine cornua as possible.

A new, and currently unresolved, issue that has been raised in this context centers on acknowledging that, in the absence of a hysterectomy, the interstitial (intramural) segment of the fallopian tube is inevitably left in situ when a bilateral salpingo-oophorectomy is performed. This portion of the fallopian tube, which resides within the muscular wall of the uterus, is very short, and part of its mucosa consists of endometrial rather than fallopian tube tissue, but theoretically there is still a concern that this fragment of retained fallopian tube carries the potential for malignant transformation. To date, there are no reports in the literature of carcinoma arising in the interstitial portion of the fallopian tube. In fact, the majority of these carcinomas occur at the distal, fimbriated end of the tube. Nonetheless, this concern has led some investigators to suggest that risk-reducing surgery in this context should include a hysterectomy.[105]

Currently, the data required to permit a fully informed decision about this choice are lacking; consequently, hysterectomy has not become a standard part of the risk-reducing surgical procedure. The increased morbidity associated with adding a hysterectomy to laparoscopic salpingo-oophorectomy must be factored into this decision as well. On the other hand, the use of MHT or tamoxifen as a breast cancer prevention strategy is considerably simplified in the absence of a uterus. If a recent preliminary report[94] suggesting a significant excess risk of endometrial cancer in *BRCA1* mutation carriers is confirmed, then the pendulum will undoubtedly swing toward including a hysterectomy. For the moment, it seems most appropriate to suggest that elective hysterectomy should at least be considered at the time risk-reducing salpingo-oophorectomy is discussed with a patient who is genetically at risk, and that this decision should be made on a case-by-case basis.

What are the epidemiologic characteristics of extraovarian primary peritoneal cancer?

Extraovarian primary peritoneal carcinoma (PPC), which is characterized by widely disseminated malignancy along the peritoneal surfaces with little or no involvement of the ovary, is also known as serous surface papillary carcinoma, papillary serous carcinoma of the peritoneum, or extraovarian peritoneal serous papillary carcinoma. Although PPC more commonly occurs in women with intact ovaries, it has also been diagnosed in women years after oophorectomy for benign conditions.[109] PPC has long been recognized as a distinctive clinical entity, but it was not until the 1990s that a formal definition was developed. The Gynecologic Oncology Group (GOG) limits the diagnosis of PPC to cases in which (1) both ovaries are physiologically normal in size or enlarged by a benign process; (2) the involvement in the extraovarian sites is greater than the involvement on the surface of either ovary; (3) ovarian involvement, if present, either (a) is confined to the ovarian surface epithelium with no evidence of cortical invasion, (b) involves ovarian surface epithelium and underlying cortical stroma but with any given tumor size less than 5×5 mm, or (c) includes tumor less than 5×5 mm within the ovarian substance with or without associated surface disease; and (4) the histology is serous mullerian.[110] Therefore, by definition, PPC is histologically indistinguishable from serous ovarian carcinoma. Some investigators have proposed broadening this definition to include other histologic types, such as endometrioid, clear cell, and mucoid.[111] Because there is no separate staging system for PPC, it is usually staged using the system for ovarian carcinoma, with most cases classified as stage III or IV.

Studies of loss of heterozygosity at various gene loci within tumor tissue have provided evidence that some PPCs are multifocal in origin.[112] A multifocal origin appears to be more common in carriers of *BRCA1* mutations[113] than in women with wild-type *BRCA1*. PPC is similar to ovarian carcinoma in terms of frequency of aneuploidy and overexpression of TP53 protein, but a higher proportion of PPCs overexpress HER-2/neu.[114]

The clinical presentation of PPC often mimics that of advanced ovarian carcinoma. In one series of 199 women with presumed ovarian cancer, 29 cases (15%) were found on laparotomy to fit the criteria for extraovarian PPC.[115] In another series, 25 of 96 patients with a preoperative diagnosis of stage III or IV ovarian adenocarcinoma were found after surgical staging to have PPC.[116]

There are few descriptive epidemiologic data available concerning PPC. A study comparing 50 women with PPC with 503 women classified as having primary ovarian carcinoma found that the former group was significantly older than the latter (mean, 64 versus 55 years). PPC was also associated with a later age at menarche (13.3 versus 12.8 years). Differences in parity between these two groups of patients did not reach statistical significance, nor were there significant

differences with regard to other ovarian cancer risk modifiers, such as OC use and family history.[117]

The association between PPC and a family history of ovarian cancer has been documented most convincingly in HBOC families. In 1982, investigators reported "intra-abdominal carcinomatosis" in 3 of 28 high-risk women who had previously undergone prophylactic oophorectomy.[118] Since then, additional cases of PPC have been documented in women with strong family histories of ovarian cancer who had their ovaries removed to decrease their risk of cancer.[119] These observations have raised questions regarding the effectiveness of oophorectomy as a risk-reducing strategy, because some women developed an ovarian cancer–like illness despite having the surgery. In one series of 324 women with strong family histories of ovarian cancer who underwent risk-reducing oophorectomy, PPC subsequently developed in 6 women.[119] The *BRCA* mutation status of these persons was not known, nor were quantitative estimates of PPC risk provided for this case series.

Molecular studies of tumor samples have linked PPC to *BRCA1*,[120] and germline mutations in *BRCA1* were found in 11% of women with PPC in one small series.[121] A larger, population-based Israeli series demonstrated that the prevalence of the Ashkenazi founder *BRCA* mutations was similar in women with PPC (28%) and in women with stage III or IV ovarian cancer (30%), regardless of family history.[122] These rates contrast with an estimated 2% carrier rate in the general Ashkenazi population. Recent data indicate that the risk of PPC is dramatically increased among carriers of *BRCA1* mutations, with an RR of 44.6 (95% CI, 24.9 to 80.2), based on 13 cases from 699 families reported to the Breast Cancer Linkage Consortium.[94]

The development of PPC after prophylactic oophorectomy in high-risk women is viewed by many as a failure of this surgical procedure to prevent ovarian cancer. Certainly, women contemplating surgical removal of their ovaries as a means to reduce the incidence of ovarian cancer need to be made aware that a modest risk of PPC will persist after surgery. However, the assertion that surgery reduces the risk of ovarian cancer by only about 50%[123] clearly represented a misinterpretation of the data cited as the basis for that estimate.[124] This error has inappropriately discouraged some high-risk patients and their health care providers concerning the potential benefit of risk-reducing surgery.

In fact, removal of the ovaries in carriers of *BRCA* mutations is associated with major reductions in both breast and BRCA-associated gynecologic cancers. In a retrospective study[125] of women with known deleterious *BRCA* mutations, 251 women who had undergone bilateral prophylactic oophorectomy were matched to 292 control women who had both ovaries intact. After excluding the 6 cases of ovarian cancer (stage I) found incidentally at the time of risk-reducing surgery, the women who underwent oophorectomy had a 96% reduction in ovarian cancer risk (HR, 0.04; 95% CI, 0.01 to 0.16). In addition, the risk of breast cancer was significantly decreased in the oophorectomy group (HR, 0.5; 95% CI, 0.3 to 0.8). The magnitude of risk reduction is impressive, even taking into account the inherent bias of the retrospective study design. In a small prospective study[126] of oophorectomy versus surveillance in *BRCA* mutation carriers with a mean follow-up time of 24.2 months, investigators found 1 case of PPC among 98 women who underwent oophorectomy, compared with 4 cases of ovarian cancer plus 1 case of PPC among the 72 women who chose surveillance. The incidence of breast cancer was also reduced in the oophorectomy group, with 3 cases diagnosed, compared with 8 cases in the surveillance group. Analyzing both breast and gynecologic cancers together, risk was reduced by 75% by oophorectomy (HR, 0.2; 95% CI, 0.1 to 0.7). Therefore, salpingo-oophorectomy is best viewed as a means to reduce (but not completely eliminate) the risk of cancer among women at increased genetic risk.

Summary

The major story regarding ovarian cancer etiology over the past 15 years is the discovery of *BRCA1/2* and the mismatch repair genes as the basis of several important genetic syndromes that underlie inherited susceptibility to ovarian cancer. These molecular advances are now being leveraged into an improved understanding of the biology of the sporadic counterpart of this disease. Such insight may translate into novel targeted therapeutic strategies.

These discoveries have also spawned a series of as yet unresolved clinical challenges regarding optimal management in genetically susceptible women, including questions about the behavior of conventional ovarian cancer risk factors in the high-risk context; the nature, timing, morbidity, and benefits associated with risk-reducing surgery; and the role of chemoprevention-based intervention strategies. The recognition of parity as a proven risk factor, and of OCs and gynecologic surgery as conferring major protection against ovarian cancer, has led to major advances in our understanding of the pathogenesis of ovarian cancer, even though the mechanism by which surgery reduces risk remains elusive.

The relationship between infertility and the risk of ovarian cancer, and that between talc exposure and ovarian cancer, remain controversial despite decades of research. Although much has been learned, there is still much work ahead in the struggle to bring this difficult disease under control. The recognition that estrogen appears to be an ovarian cancer risk factor and that progestins represent a promising risk-reducing option is shaping the direction of chemoprevention research for this cancer.

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